Claim 79, line 2, after "IGIF", insert --protein--.

Claim 80, line 2, after "IGIF", insert --protein--.

Claims 86, line 1, before "antibody", delete "An" and insert therefor --A polyclonal--.

REMARKS

The Office Action and the cited and applied references have been carefully studied. No claims are allowed. Claims 56 and 59-92 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 69-80, 83, 84, and 88 have been rejected under the judicially approved doctrine of nonstatutory double patenting as being unpatentable over claim 2 of U.S. Patent 5,912,324. The examiner holds that, although the conflicting claims are not identical, they are not patentably distinct from each other because they encompass common subject matter and/or obvious variations thereof.

This rejection is obviated by the terminal disclaimer attached hereto.

Claims 59-67, 69-72, and 74-80 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner indicates that changing the recitation of "hybridized" to "hybridizes", in claim 59 will clarify the claims and overcome this rejection. Claim 59 is amended to delete the recitation of

"hybridized", thereby obviating this rejection. New claim 89, which uses the present tense "hybridizes", avoids this indefiniteness issue.

Claims 56 and 59-88 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al. (*Infect. Immun.* 61:64-70, 1993) in light of counsel's concessions made during the prosecution of parent application serial no. 08/502,535, now U.S. Patent No. 5,912,324.

The examiner states that Nakamura describes a purified IL-12-like factor (abstract) which migrates at 70-75 kDa on gel filtration and at 50-55 kDa on SDS-PAGE (page 68, column 2, second paragraph) and compositions comprising this factor and various other substance in PBS (page 53, paragraph bridging columns) induce the production of IFN-γ in resting T and NK cells (abstract).

The examiner asserts that although Nakamura teaches that the factor it describes is apparently homogeneous and has a molecular weight outside of the range specified in claim 1, the prior art factor appears to meet the limitation of claim 1 for the following reasons. As evidenced by Okamura et al. (*Infect. Immun.* 63:3966-3972, 1995), which lists several authors in common with the Nakamura reference, the examiner holds that an 18-19 kDa IFN-γ inducing factor is a component of the 70-75 kDa factor known in the prior art, citing Okamura's disclosure in the paragraph bridging pages 3970-71:

> This factor was purified from [a murine] liver extract .... Its isoelectric point

> determined by Mono P column chromatography was 4.8 .... Unexpectedly, the IGIF that was previously found in the sera of mice and that caused endotoxic shock ([citation to the Nakamura paper and an earlier publication]) was shown to contain the same molecule as was purified from the liver extract (Fig. 5). ... [T]he molecular form of IGIF in serum remains unknown. It may exist in an oligomeric form or may be bound to another molecule.

It is noted by the examiner that a later paper from the same laboratory (Ushio et al., *J. Immunol.* 156:4274-4279, 1996) evidences that the 18-19 kDa murine factor described in the Okamura paper has an amino acid sequence (Fig. 2) which is identical to that shown in instant SEQ ID NO:2. In view of the similar sources and the identity of structural, biophysical, and functional properties of the instantly claimed protein and the 18-19 kDa factor described in the Okamura and Ushio papers, it reasonably appears to the examiner that they are the same.

The examiner indicates that the only arguable difference between Nakamura and original claim 1 to be addressed is the molecular weight. The 18-19 kDa molecular weight is said to be an inherent property of the IGIF gene product, as evidenced by Okamura and Ushio. The examiner asserts that the limitations of the claim are met if the recited product is identified in the prior art; it does not require that the 19 kDa factor be homogeneous or otherwise purified. Because the characteristic biological properties of mIGIF are identified in the prior art, the examiner takes the position that the prior art complex inherently meets the

limitations of the claim insofar as it comprises a discrete 18-19 kDa component.

The examiner further asserts that Nakamura additionally provides evidence which the ordinarily skilled artisan would have interpreted to convey the existence of a factor having the activities described and a molecular weight of ca. 21-22 kDa, citing Fig. 2 at page 67 for depicting the electrophoretic separation of the IGIF marked a, b, c, and d. The examiner specifically states that, notwithstanding the description in the text of a molecular weight on SDS-PAGE of 55 kDa, the active fraction identified in the figure aligns between the 21 and 23 kDa molecular weight markers in lane d. This evidence is taken by the examiner to indicate that Nakamura describes a factor inherently having all of the physicochemical properties required by claim 1 and it fully describes the biological activity required as a limitation of the claim.

It is the examiner's position that, because Nakamura describes the protein of original claim 1, including its biological activity, a monoclonal antibody specific for that protein is obvious under 35 U.S.C. §103 as a matter of law, per counsel's express concession. To the extent that Nakamura is ambiguous as to the molecular weight and to the extent that claim 1 cannot be fairly construed to read on a material which is said to exhibit a molecular weight outside the recited range, the examiner indicates that counsel's concession nonetheless weighs in favor of the conclusion that the genus

of monoclonal antibodies specific for the Nakamura IGIF material is obvious under §103. The examiner further indicates that, in addition to conceding the obviousness of a mAb to "the protein of claim 1," counsel stated in the reply of 14 February 1997 that "[t]echniques of raising monoclonal antibodies are well known" and that "[k]nowing the biological activity of such protein [as the protein of claim 1], one of ordinary skill in the art would have been motivated to make a monoclonal antibody for the purpose of immunoaffinity chromatography or for the purpose of blocking its activity. The techniques for doing so are well known." These concessions are said to be generic in nature.

The examiner holds that, because the 18-19 kDa IGIF is at the least a significant component of the 55/75 kDa material described by Nakamura (Okamura considers the possibility that Nakamura observed a multimer), a significant number of the antibodies within the genus conceded to be obvious in view of it would have recognized epitopes on the 18-19 kDa component. Furthermore, the examiner states that the prior art teaches the biological activity which counsel is said to have conceded that it would have been obvious to block using a conventionally made monoclonal antibody, and the evidence of record indicates that the biological activity is associated with the 18-19 kDa component of the prior art material. It is therefore the examiner's determination that counsel has conceded the obviousness of the genus of monoclonal antibodies specific for the Nakamura IGIF and has

further conceded that it would have been obvious to select from that genus the subgenus of antibodies capable of blocking the activity described in the prior art. The examiner further states that, because the evidence of record indicates that such antibodies would meet all of the limitations of the instant claims, such claims are consequently held to be unpatentable under 35 U.S.C. §103. This rejection is respectfully traversed.

It is submitted that counsel has not made the concession that all monoclonal antibodies to a known protein are obvious, merely that, in general, it would be obvious to make antibodies to a known protein. Nevertheless, counsel's statements made in the parent application are irrelevant here because, while it would be obvious to make antibodies to the 55-75 kDa purified IFN-γ inducing factor reported by Nakamura, this is not the case for the 19 kDa IGIF protein, the existence of which was not known or reported in the prior art. How would it be obvious to make antibodies to an unknown protein, even if this unknown protein has the same functional activity of Nakamura's 55-75 kDa prior art factor? Thus, while it may be obvious to make antibodies to Nakamura's 55-75 kDa, antibodies according to the present invention, which are specific to the 19 kDa IGIF protein, are unobvious in view of the prior art.

The examiner's position appears to be that it would be obvious to make an antibody to the 55-75 kDa factor of Nakamura and to block its IFN-γ inducing activity with such an

antibody because the 19 kDa IGIF protein recited in the present claims is inherently contained in the larger molecular weight 55-75 kDa factor of Nakamura.

The examiner refers to the teachings of Okamura in his rejection. However, as specifically stated by Okamura,

> [T]he molecular form of IGIF in serum remains unknown. It may exist in an oligomeric form or may be bound to another molecule.

Thus, it is only with hindsight that one of ordinary skill in the art would realize that the 19 kDa IGIF protein is contained in the larger 55-75 kDa factor. Without this bit of hindsight, one of ordinary skill in the art in search of a monoclonal antibody which blocks the IFN-γ inducing activity of Nakamura's 55-75 kDa factor would be satisfied when the first such monoclonal antibody is obtained. One would not have any further motivation to search for more antibodies which block IFN-γ inducing activity.

Because the form of Nakamura's 55-75 kDa factor is unknown, it is completely unpredictable whether or not an antibody that blocks the IFN-γ inducing activity of the 55-75 kDa factor would also block the IFN-γ inducing activity of the 19 kDa factor. There are a number of reasons why a monoclonal antibody that blocks the inducing activity of a larger factor, whether it is a complex or an oligomer would not block the inducing activity of a smaller factor contained therein. For example, there may be different conformations present in the larger factor which would not be present in the smaller

factor. In addition, the anti-55-75 kDa factor antibody may only sterically block access to the IFN-γ inducing "active site" by binding to an epitope that is not present or available on the 19 kDa factor. Accordingly, there is no predictability that an antibody which blocks IFN-γ inducing activity of the 55-75 kDa factor would similarly block the IFN-γ inducing activity of the 19 kDa factor. One of ordinary skill in the art, unaware of a smaller active factor that may be contained in Nakamura's 55-75 kDa factor, would be quite satisfied once a monoclonal antibody that blocks the IFN-γ inducing activity of Nakamura's factor is obtained and would have no motivation to search any further.

As further evidence that there is a difference between Nakamura's 55-75 kDa factor and the 19 kDa IGIF recited in the present claims, the present specification discloses on page 23, lines 9-15, that the 19 kDa protein band has IFN-γ inducing activity on SDS-PAGE, whereas Nakamura specifically teaches on page 68, right column, second paragraph, that Nakamura's 55-75 kDa factor lost its activity on SDS-PAGE.

With regard to the examiner's assertion that, notwithstanding the description in the text of the Nakamura reference of a molecular weight of 55 kDa on SDS, the active fraction in Fig. 2, lanes a (upper band) and d, it is respectfully submitted that the examiner's interpretation is incorrect. As the copy of the Nakamura reference in the file of record appears to be of poor quality, attached hereto is a

better quality copy of the applied Nakamura reference to make clear what is being shown in Fig. 2. Applicants point out that the molecular weight markers in lane d only provide markers for lane c because both are run on the same SDS-PAGE gel, whereas lanes a and b are run on separate PAGE (no SDS) gels. Thus, while the graph of activity (IFN-γ titers) versus gel slice number in Fig. 2 is aligned with PAGE lanes a and b, this is not the case (nor is it intended to be) with the molecular weight markers on SDS-PAGE. As is well-recognized in the art, proteins in the presence of SDS assume a random-coil configuration and all such SDS-cladded random coils have the same ratio of charge to mass ratio which permits reasonably accurate correlation with SDS-cladded molecular weight markers. It is quite clear to those of skill in the art that the molecular weight of the bands in PAGE gel lanes a and b cannot be aligned with SDS-PAGE molecular weight markers to determine molecular weight of non-SDS-cladded proteins. Accordingly, Fig. 2 of Nakamura does not disclose or teach an active fraction in the 21 to 23 kDa range, as asserted by the examiner, and therefore does not contradict what is disclosed in the text of the Nakamura reference on page 66, right column.

As pointed out above, there is absolutely no predictability that such a monoclonal antibody would also block IFN-γ inducing activity of the 19 kDa factor, and there would also be no motivation to look for those antibodies that would recognize, or even more specifically block, the IFN-γ

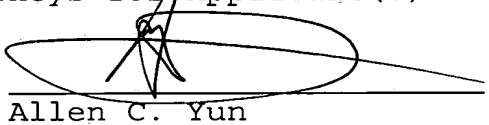
inducing activity of the smaller 19 kDa IGIF protein. Accordingly, the presently claimed invention cannot be made obvious by the prior art.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By: 
Allen C. Yun
Registration No. 37,971

ACY:pr

624 Ninth Street, N.W.
Suite 300
Washington, D.C. 20001
Facsimile: (202) 737-3528
Telephone: (202) 628-5197

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